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VIA FEDERAL EXPRESS

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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Draft Guidance for Industry on Applications Covered by Section 505(b)(2) – Docket No. 99D-4809

Dear Sir or Madam:

McKenna & Cuneo, L.L.P. submits these comments concerning the above referenced draft guidance document on behalf of an unnamed pharmaceutical manufacturer. These comments serve two purposes: (1) to support the Food and Drug Administration's (FDA's) position with respect to the draft guidance; and (2) to respond to recent comments submitted to this docket that question the legality of the agency's 505(b)(2) application policy.

Our client supports the FDA's attempt to clarify the scope of section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA). The draft guidance merely restates FDA's longstanding policy with respect to 505(b)(2) applications. As such, our client generally supports the draft guidance and recommends that it be finalized as soon as possible.

Although the draft guidance does not state any new FDA policies, recent comments to this docket by the Pharmaceutical Research and Manufacturers of America (PhRMA) and Pfizer, Inc. (Pfizer) have questioned the legality of the agency's positions. As a pharmaceutical manufacturer who foresees the possibility of filing 505(b)(2) applications in the future, our client feels compelled to respond to the arguments put forth by PhRMA and Pfizer, particularly the assertions that FDA is prohibited from relying upon previous findings of safety and effectiveness,

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and that the draft guidance will somehow allow drug products to be approved under a less rigorous safety and efficacy standard.

As discussed in greater detail below, FDA has correctly interpreted section 505(b)(2) to allow the agency to rely on the safety and efficacy data in a previously approved new drug application (NDA) to support (in whole or in part) the approval of a 505(b)(2) application, even if the applicant has not received a right of reference from the NDA holder. Likewise, FDA has correctly recognized that the 505(b)(2) application process is unrelated to the scope of the agency's review of a given drug product. 505(b)(2) applicants must meet the same rigorous safety and efficacy standards as "full" NDA applicants. The only difference is the source of the information. With respect to both of these issues, FDA has been faithful to the statute and authority granted to it by Congress. PhRMA and Pfizer's assertions are based on a flawed reading of the plain language of the statute and would result in unnecessary and duplicative clinical studies.

I. FDA Has Correctly Interpreted Section 505(b)(2) to Allow Approval of Applications Based on the Agency's Prior Finding of Safety and Efficacy

The statutory language of section 505(b)(2) is very simple. A 505(b)(2) application is described as

> an application submitted under [section 505(b)(1)] for a drug for which the [full reports of safety and efficacy investigations] relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted. . . .

21 U.S.C. § 355(b)(2). In the draft guidance, FDA interprets this provision to allow 505(b)(2) applicants to rely on a previous FDA finding of safety and effectiveness for an approved drug product. See Draft Guidance at 2. This interpretation is consistent with the statutory language and intent of the Waxman-Hatch Amendments, FDA's regulations, and the agency's longstanding policies.

A. The Draft Guidance is Consistent With the Statutory Language and Legislative Intent

Section 505(b)(2) contains no limitation on the source of information that may be referenced by a 505(b)(2) applicant. It simply states that a 505(b)(2) applicant may meet a portion of the NDA requirements (i.e., full reports of safety and effectiveness) by unauthorized reference to other sources. Congress left it to FDA to determine what other sources would be acceptable. However, FDA was not left entirely without Congressional guidance. Section 505(b)(2), like all statutory provisions, cannot be read in isolation. It was enacted as part of the Drug Price Competition and Patent Term Restoration Act of 1984 (the "Waxman-Hatch Amendments") and contains patent certification and market exclusivity restrictions that are identical to those applicable to abbreviated new drug applications (ANDAs). *See* FDCA § 505(j). Like section 505(b)(2), section 505(j) does not contain an express authorization for FDA to reference the data contained in approved NDA files. Yet, even PhRMA does not question that Congress intended FDA to do just that when reviewing ANDAs. As such, FDA has taken the only plausible interpretation of section 505(b)(2) when the statutory language is read in the context of the entire Waxman-Hatch Amendments.

It is well documented that the Waxman Hatch Amendments were intended to strike a balance between the competing interests of ensuring the development of new drug products and providing the public with affordable, quality drug products. In striking that balance, Congress gave the branded industry protection from competition in the form of market exclusivity and patent term extensions. In exchange, ANDA and 505(b)(2) applicants received the ability to rely on the data contained in approved NDA files to support approval of their applications. Yet, PhRMA suggests that FDA should upset this delicate balance by limiting 505(b)(2) applications to only references to published data in the public domain. It is impossible to square such an interpretation with the language and intent of the statute. Without the ability to reference data from previously approved applications, the *quid pro quo* that Congress intended for the 505(b)(2) process would be lost. Neither the public nor 505(b)(2) applicants gain anything from the ability to reference public literature because FDA permitted the reference to published articles before the Waxman-Hatch Amendments were enacted. Thus, the branded industry is arguing that Congress intended to give it a free government imposed monopoly at the expense of the public, even when there are no patent or exclusivity protections available. Such a reading of the statute is not only

inconsistent with the language of the statute and the intent of Congress, it is simply unfair.

With respect to the relevant legislative history, Pfizer and PhRMA assert that section 505(b)(2) was intended to do nothing more than codify the FDA's "paper NDA" policy.[1] They argue that "paper NDAs" only allowed references to published literature and that 505(b)(2) applications should be similarly limited. As noted above, such a narrow construction of the statute runs counter to the fundamental purposes of Waxman-Hatch Amendments, namely to grant the branded industry patent and exclusivity protection and to ensure affordable drug products while avoiding unnecessary duplicative clinical trials. FDA has already considered the legislative history cited by PhRMA and Pfizer and correctly concluded that section 505(b)(2) was intended to be broader than the paper NDA policy. *See* 54 Fed. Reg. 28872, 28890 (July 10, 1989). For example, the "paper NDA" policy was limited to "duplicate" drug products, while section 505(b)(2) contains no such limitation. Therefore, PhRMA's and Pfizer's references to the legislative history and the use of the term "paper NDA" are totally misplaced. The agency has long since settled the issue that the scope of section 505(b)(2) is not to be construed using the limited paper NDA policy.

Additionally, FDA was well within its statutorily defined role when it published the draft guidance. Taken in their best light, PhRMA's arguments would only prove ambiguity in section 505(b)(2) with respect to whether FDA can reference prior findings of safety and effectiveness. When faced with such ambiguity, it is FDA's statutory obligation to interpret the statute in a manner that implements the intent of Congress. Furthermore, the federal courts are compelled to uphold the agency's interpretation so long as it is a "permissible construction of the statute." *See Chevron v. NRDC,* 467 U.S. 837, 842-43 (1984). As noted above, the FDA's

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[1] The "paper NDA" policy allowed FDA to approve drugs that were duplicates, or near duplicates, of drug products that were approved after 1962 based on scientific literature. Prior to Waxman-Hatch Amendments, abbreviated new drug applications (ANDAs) were available only to pre-1962 drugs. See 46 Fed. Reg. 27396 (May 19, 1981)

policy is more than "permissible," it is compelled by the plain language, underlying intent, and overall context of the Waxman-Hatch Amendments.

B. The Draft Guidance is Consistent With Longstanding FDA Policies

It has been FDA's policy since the enactment of the Waxman Hatch Amendments that 505(b)(2) applicants could rely on previous findings of safety and effectiveness. Although Pfizer asserts that "the Agency itself has recognized that the Act does not authorize the approval of 505(b)(2) applications based on an innovator's safety and effectiveness data," that assertion is patently false. Pfizer comment at 4. The very document cited by Pfizer to support its assertion (the preamble to the ANDA proposed rule) states that "FDA is proposing to treat as a 505(b)(2) application an application for a change in an already approved drug supported by a combination of literature or new clinical investigations *and the agency's finding that a previously approved drug is safe and effective.*" 54 Fed. Reg. at 28891 (emphasis added).

Furthermore, FDA's regulations explicitly state that the approval of a 505(b)(2) application may be supported by the agency's previous finding of safety and effectiveness. The agency's regulations require 505(b)(2) applicants to identify the approved listed drug "for which FDA has made a finding of safety and effectiveness and on which finding the applicant relies in seeking approval of its proposed drug product." 21 C.F.R. § 315.54(a)(1)(iii). Pfizer argues that this regulation only permits the authorized reference of approved NDAs because FDA did not specifically state that unauthorized use was allowed. *See* Pfizer comment at n.3. Pfizer fails to explain, however, why a regulation that contains the requirements for filing 505(b)(2) applications would address only authorized references to approved NDAs when, by definition, 505(b)(2) applications involve only unauthorized references. Applications that contain authorized references to approved products are submitted under section 505(b)(1), not 505(b)(2), and therefore would not be the subject of 21 C.F.R. § 315.54.

C. The Draft Guidance Represents Sound Public Policy

FDA's policy of allowing reference to previously approved NDAs is consistent with FDA's mandate to protect the public from unnecessary health risks. By allowing 505(b)(2) applicants to rely on FDA's prior findings of safety and effectiveness, FDA is preventing unnecessary and duplicative clinical trials to prove

what is already known about FDA approved drug products. Requiring duplicative studies would place study subjects at risk without any scientific justification for doing so.

The draft guidance also benefits the public by encouraging the development of innovative variations of approved drug products. The rigid ANDA process allows very little variation from the listed drug. In contrast, section 505(b)(2) allows applicants to reference the existing knowledge base and build upon it in ways that could be beneficial to the public. If 505(b)(2) applicants were not able to reference the data in approved NDA's, the time and expense associated with having to repeat the safety and efficacy studies conducted by the NDA holder would act as a significant disincentive to the research and development of innovative improvements to existing drug products.

Furthermore, FDA's reference to previous findings of safety and efficacy would not affect NDA holders intellectual property rights. NDA holders have the same intellectual property protections against 505(b)(2) applicants that they have against ANDA applicants. 505(b)(2) applicants must file patent certifications with their applications. If they seek approval before the NDA holder's patents expire, they must file a paragraph IV certification and the NDA holder gets the benefit of an automatic 30 month statutory injunction while the patent litigation proceeds. If the court determines that the 505(b)(2) applicant's product infringes on the NDA holder's patent, the 505(b)(2) application cannot be approved. Thus, NDA holders are given ample opportunity to defend their patents against infringing products, and it is axiomatic that NDA holders are not entitled to additional protection from non-infringing products.

II. The Draft Guidance is Consistent with the Supreme Court's Interpretation of the Takings Clause of the Fifth Amendment to the U.S. Constitution

FDA's reference to previous findings of safety and effectiveness is not an unconstitutional "taking" of private property. While the data submitted in an NDA is private property that may be subject to trade secret protection, the agency's reference to the data when reviewing a 505(b)(2) application does not effect a

"taking" of that property because the submitter of the data was "on notice" that the data could be referenced by the FDA when the data was submitted. *See Ruckelshaus v. Monsanto*, 467 U.S. 986 (1984)[2] As noted above, the plain language of section 505(b)(2) made it clear to NDA applicants in 1984 that their data may be used by the agency to approve 505(b)(2) applications. Any NDA holders who do not receive the message from the statute were clearly placed on notice by FDA's regulations and the associated *Federal Register* notices. *See* 21 C.F.R. § 315.54; *see also* 54 Fed. Reg. 28872 (July 10, 1989) and 57 Fed. Reg. 17950 (Apr. 28, 1992).

Furthermore, the cases cited by Pfizer in its comments to this docket support the position taken by the FDA in the draft guidance. The *Monsanto* case supports the proposition that a "taking" only occurs when the submitter of the data has a "reasonable investment-backed expectation" that the agency will not reference the submitted data when reviewing other applications. *See Monsanto* 467 U.S. at 1006. In that case, the Supreme Court held that Monsanto had such an expectation during the period when the statute explicitly assured them that their data would not be referenced by the Environmental Protection Agency ("EPA"). Thus, the court held that EPA effected an unconstitutional taking of Monsanto's trade secret property. However, the court also held that no taking occurred with respect to data submitted during the period when the statute was silent as to the EPA's use of the data, or when the statute authorized such agency use. *Id.* at 1007-1009. In language equally applicable to the submission of an NDA, the court stated "as long as Monsanto is aware of the conditions under which the data are submitted, and the conditions are rationally related to a legitimate Government interest, a voluntary submission of data by an applicant in exchange for the economic advantages of a

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[2] The FDA's position on 505(b)(2) applications is also consistent with the agency's position on device premarket approval applications (PMAs). FDA recently interpreted section 216 of the Food and Drug Administration Modernization Act (FDAMA), which allowed FDA to reference data in approved PMAs after 6 years, as allowing the agency to reference data in applications submitted after November 28, 1990. That date was selected because the agency determined that it was the date upon which PMA applicants were placed "on notice" that the data in their PMAs may be referenced by the agency. *See Guidance on Section 216 of the Food and Drug Administration Modernization Act of 1997* (August 9, 2000).

registration can hardly be called a taking." *Id* at 1007 (*citing Corn Products Refining Co. v. Eddy*, 249 U.S. 427, 431-432).

Likewise, the *Tri-Bio Laboratories v. FDA* case cited by Pfizer, to the extent that it is even relevant to the FDA's 505(b)(2) policy, is consistent with the *Monsanto* decision. *See Tri-Bio Laboratories v. FDA*, 836 F.2d 135 (3rd Cir. 1987). In that case, Tri-Bio sought FDA approval of its generic animal drug product based on the safety and efficacy data contained in the innovator's approved new animal drug application ("NADA"). Based on FDA's stated policy and its regulations (21 C.F.R. § 514.1(a)), the agency refused to allow Tri-Bio to rely on the previously approved data. The court held that FDA's regulation provided the "reasonable investment-backed expectation" required under *Monsanto*. Therefore, FDA was correct in its assertion that referencing the approved NADA would constitute an unconstitutional taking.

FDA's 505(b)(2) policy, however, presents a very different situation from that faced by the court in *Tri-Bio Laboratories*. In fact, it is the very opposite of the *Tri-Bio* fact pattern. Both the plain language and the legislative history of the Waxman-Hatch Amendments provide clear guidance to FDA concerning the intent of section 505(b)(2). Likewise, and in contrast to the animal drug regulations addressed in the *Tri-Bio* case, FDA has a specific regulation informing NDA holders that the agency may rely on the safety and efficacy data in their application to approve a 505(b)(2) application. *See* 21 C.F.R. § 314.54. Therefore, NDA holders who submitted their applications after the enactment of the Waxman-Hatch Amendments could not possibly have had a reasonable expectation that the agency would not reference their data. The *Tri-Bio* case only supports such a conclusion.

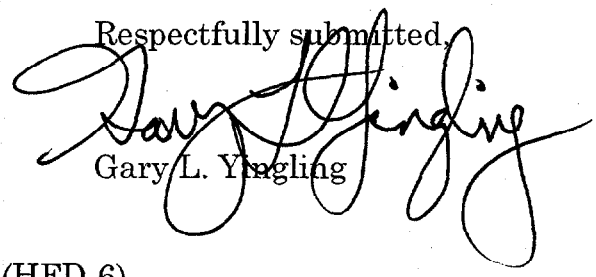
III. The Draft Guidance Ensures That 505(b)(2) Applications Will Be Reviewed Under The Same Standards of Safety and Efficacy as "Full" NDAs

FDA correctly recognized that it would be impracticable to address every possible type of 505(b)(2) application in its guidance document. Therefore, the draft guidance lays out the general types of applications that are possible without attempting to specifically state what will be required for each application. PhRMA and Pfizer object to this approach and allege that the agency has established a lower standard for 505(b)(2) applications. These allegations are thinly disguised attempts to inject a safety issue where none exists.

FDA has long recognized that 505(b)(2) applications must meet the same rigorous requirements as "full" NDAs submitted under section 505(b)(1). *See* 54 Fed. Reg. at 28892. In fact, the statute describes 505(b)(2) applications as "applications submitted under [505(b)(1)]." FDA has the requisite expertise to determine what additional data, if any, is needed to support the approval of a 505(b)(2) application. Because the possibilities are nearly endless, that determination is best made on a case-by-case basis after the agency has reviewed the supporting references in light of the differences between the proposed and approved products.

In closing, our client commends the FDA on its effort to provide additional guidance on the agency's 505(b)(2) policy. The draft guidance is consistent with both the plain language and intent of the FDCA, and expresses sound public policy. Should the agency have any questions concerning these comments, please contact the undersigned at (202) 496-7645.

Respectfully submitted,



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cc: Khyati N. Roberts, CDER (HFD-6)

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